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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,778	06/28/2001	Tongtong Wang	210121.455C16	1354

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/01/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/897,778	Wang et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 7, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-6, 9-11, and 13-23* is/are pending in the application.

4a) Of the above, claim(s) *1, 3-6, 9-11, and 15-19* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13, 14, and 20-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, 8, 10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of group II, claims 2, 7, 8 and 12-14, in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.E.P.. § 818.03(a)).

2. Claims 1, 3-6, 9-11 and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 12.

Claims 13 and 14 have been amended. Claims 2, 7, 8 and 12 have been canceled. Claims 20-23 have been added. Claims 1, 3-6, 9-11 and 13-23 are pending and claims 13, 14 and 20-23 are under consideration.

Priority

The polypeptide sequence of SEQ ID No. 176 has only been disclosed in Application Nos. 09/466,396, 09/476,496, 480,884 etc., and up in the listing of its parent applications but has not been disclosed in the parent Application Nos preceding 09/466,396. Therefore, the priorities claimed from the parent US Application Nos preceding 09/466,396, for example Application No. 09/285,479, are not granted. Thus, SEQ ID No. 176 of the present application has the priority date of Application No. 09/466,396, filed 12-17-99.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: whether the administered composition stimulates an immune response in the patient.

5. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: whether and what type of therapeutic effect has been obtained in the patient.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 13, 14, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13, 14, 20 and 21 are directed to an immunogenic composition comprising an adjuvant and a polypeptide having at least 90% identity to the amino acid sequence of SEQ ID No. 176, and a method of using said polypeptides for stimulating immune response or for treatment of a cancer in a patient.

The claims read on a genus of polypeptides comprising an amino acid sequence having at least 90% identity to the sequence of SEQ ID No. 176. The specification only discloses a amino acid sequence SEQ ID NO. 176. The claims encompass adding unknown and unidentified amino acid sequence to the 5', 3' end and/or within SEQ ID No. 176 that result in various unknown and unidentified polypeptides having different biological functions.

The scope of the claim includes numerous structural variants of SEQ ID No. 176, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide any structural feature that is essential to the biological function of the amino acid sequence of SEQ ID No. 176. Structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly

variant, the polypeptide sequence SEQ ID No. 176 as disclosed in the present application is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed polypeptide sequences. Thus, it is concluded that the written description requirement is not satisfied for the genus of polypeptides and their uses in the claimed method.

8. Claims 13, 14, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising SEQ ID No. 176 or comprising residues 37-55 or 41-51 of SEQ ID No. 176, does not reasonably provide enablement for an immunogenic composition comprising any portion of SEQ ID No. 176 other than the disclosed residues 37-55 or 41-51 of SEQ ID No. 176, or an immunogenic composition comprising a polypeptide having at least 90% identity to SEQ ID No. 176 or a portion thereof, a method for stimulating an immune response in a patient with said immunogenic composition, and a method for treating a lung cancer in a patient by using an immunogenic composition comprising a polypeptide having the sequence of SEQ ID No. 176 or a portion thereof or a polypeptide having at least 90% identity to SEQ ID No. 176 or a portion thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 13, 14, 20 and 21 are directed to an immunogenic composition comprising an adjuvant and a polypeptide having at least 90% identity to the amino acid sequence of SEQ ID No. 176 or a portion thereof, and a method of using said polypeptides for stimulating immune response or for treatment of a cancer in a patient.

The specification only discloses the amino acid sequence SEQ ID NO. 176 and overexpression of the amino acid sequence of SEQ ID No. 176 in lung cancer cells as compared to normal cells, and identifies epitopes amino acid residues 37-55 and 41-51 of SEQ ID No. 176 that are recognized by CD8+ T cells (specification, p. 167, 168). The claims encompass adding unknown and unidentified amino acid sequence to the 5', 3' end and/or within SEQ ID No. 176 that result in various unknown and unidentified polypeptides having different biological functions. The scope of the claim encompasses the use of numerous structural variants of SEQ ID No. 176 and a portion thereof to stimulate an immune response or to treat a lung cancer in a patient.

The specification fails to provide adequate guidance and evidence for whether administration of a composition comprising the claimed polypeptides or a portion thereof can stimulate immune response in a patient. The specification also fails to provide any structural feature that is essential to the biological function of the amino acid sequence of SEQ ID No. 176 or to provide any epitope region (antigen determinant) within SEQ ID No. 176 and its variants other than the disclosed amino acid residues 37-55 and 41-51 of SEQ ID No. 176 that can stimulate immune response in a patient. Ten % of 579 amino acid residues accounts to about 58

amino acid difference within the amino acid sequence of SEQ ID No. 176. The claims encompass numerous polypeptides and a portion thereof that differ dramatically from the amino acid sequence of SEQ ID No. 176, and the biological functions and antigen determinants for stimulating immune response could vary dramatically from SEQ ID No. 176 and the disclosed amino acid residues 37-55 and 41-51 of SEQ ID No. 176.

It was known in the art that an antibody binds to an antigenic site, i.e. antigenic determinants or epitopes, on a protein and the antigenic site on a protein was unpredictable at the time of the invention from mere amino acid sequence. Stern, 1991 (TIBTECH, Vol. 9, p. 163-169) states that protein characteristics immunogenicity (the ability to generate antibodies) and antigenicity (the ability to be recognized by antibodies) are necessary and sufficient for a selected peptide to be effective as an antigen capable of raising antibodies recognizing the native protein. All antigenic sites are considered to be conformational that could be continuous or discontinuous in which the residues of the epitope may not be continuous but are brought together by folding into the three dimensional structure of the protein (e.g. p. 163, middle column). Stern points out that "Using the three-dimensional structure is more reliable since it includes the predominant factors in antigenicity-mobility and surface topography. Unfortunately...prediction algorithms based on the far more extensive database of primary sequences are less successful". "The major drawback of using hydropathicity to predict antigenicity is that not all antigenic sites are hydrophilic, and that usually only the highest peak can be reliably used to predict epitopes (e.g. p. 164, right column). "Prediction methods which rely only upon the amino acid sequence of the

protein can only succeed in so far as antigenicity is sequence determined...but...sequence alone is not necessarily a determinant of immunogenicity (e.g. p. 167, left column).

Further, Greenspan et al., 1995 (Immunology Today, Vol. 16, No. 5, p. 226-230) reports that "Structural elements of an antibody (Ab) or antigen (Ag) distant from the actual sites mediating contact between Ab and Ag can exert substantial influence on binding to, and discrimination among, multivalent targets" (see abstract). The three-dimensional structure or the conformation of a protein plays an important role in determining the antigenic site of a protein. A portion of SEQ ID No. 176 or its various variants could vary dramatically from amino acid residues 37-55 and 41-51 of SEQ ID No. 176 and whether said portion can stimulate immune response in a patient was unpredictable at the time of the invention. Thus, one skilled in the art at the time of the invention would not know how to use the claimed polypeptide or a portion thereof to stimulate immune response in a patient.

The specification fails to provide adequate guidance and evidence that administration of the claimed composition could provide therapeutic effect for a particular disease or disorder in a patient, such as a lung cancer. The specification also fails to provide adequate guidance for the correlation between the stimulation of immune response in a patient and a particular disease.

As discussed above, the claims encompass numerous polypeptides and a portion thereof that differ dramatically from the amino acid sequence of SEQ ID No. 176, and the biological functions and antigen determinants for stimulating immune response could vary dramatically from SEQ ID No. 176 and the disclosed amino acid residues 37-55 and 41-51 of SEQ ID No.

176, and whether said polypeptides and a portion thereof can stimulate immune response in a patient was unpredictable at the time of the invention. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, it would be unpredictable for the biological functions of

the claimed polypeptides from mere amino acid sequences. Absent the detailed structural information of antigen determinants of SEQ ID No. 176 and its variants and the intended disease for stimulating immune response in a patient, and unpredictability of protein function from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the claimed polypeptides or a portion thereof to stimulate an immune response in a patient such that said immune response provide therapeutic effect for a particular disease or disorder in said patient and would have to engage in undue experimentation to practice over the full scope of the invention claimed.

Claim 14 reads on treating a lung cancer in a patient with the claimed polypeptides or a portion thereof. No biological function of the polypeptide sequence of SEQ ID No. 176 has been described. The claims encompass adding unknown and unidentified amino acid sequence to the 5', 3' end and/or within SEQ ID No. 176 that result in various unknown and unidentified polypeptides having different biological functions. The scope of the claim includes numerous structural variants of SEQ ID No. 176 and a portion thereof.

The specification fails to provide adequate guidance and evidence for how to administer the composition comprising the claimed polypeptide or a portion thereof to a patient and whether the administration of said composition would provide therapeutic effect in treating a lung cancer in said patient.

As discussed above, the biological function of a protein is unpredictable from mere amino acid sequence. Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of

Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Similarly, the administration routes, the stability of the polypeptide administered, the altered polypeptide function within the target cells, and the amount of polypeptide that reaches the target cells are all important factors for a successful cancer therapy using a composition comprising a polypeptide or a portion thereof.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working example provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 20-23 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen et al., WO 99/54738.

Claims 20-23 are directed to an immunogenic composition comprising an adjuvant and a polypeptide comprising the sequence of SEQ ID No. 176 or a portion thereof, or a polypeptide having at least 90% identity to SEQ ID No. 176, or specifically comprising residues 37-55 or 41-51 of SEQ ID No. 176.

Chen teaches a composition comprising the cancer associated antigens, CT7, KOC-2 and KOC-3, and a pharmaceutically acceptable adjuvant, and related cancer associated protein KOC-1. Chen teaches that each of those antigens provides antibodies when expressed in a subject. KOC-1 is highly overexpressed in pancreatic cancer cells as compared to normal pancreatic cells and has amino acid sequence that is 100% identical to the sequence of SEQ ID No. 176 (see computer printout page 1-2, Mueller-Pillasch, 1997, SPTREMBL Accession No. O00425, and

Mueller-Pillasch et al., 1997, Oncogene, Vol. 14, p. 2729-2733). The disclosed KOC polypeptide sequence comprises residues 37-55 or 41-51 of SEQ ID No. 176. Although Chen does not specify what adjuvant to be used for the composition comprising KOC polypeptide, it would have been obvious for one of ordinary skill to use the adjuvants recited in claim 21 since they were known in the art at the time of the invention. Thus, claims 20-23 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen et al., WO 99/54738.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen